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Imino Transfer Hydrogenation Reductions.

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Abstract: This review contains a summary of recent developments in the transfer hydrogenation of C=N bonds, with a particularly focus on reports from within the last 10 years and asymmetric transformations. However earlier work in the area is also discussed in order to provide context for the more recent results which are described. There is strong focus on the Ru/TsDPEN class of asymmetric transfer hydrogenation reactions originally reported by Noyori *et al.*, together with examples of their applications, particularly to medically-valuable target molecules. The recent developments in the area of highly active imine-reduction catalysts, notably those based on iridium, are also described in some detail. There is a discussion of diastereoselective reduction methods as a route to the synthesis of chiral amines using transfer hydrogenation. The recent development of methodology for positioning reduction complexes within chiral proteins, permitting the generation of asymmetric reduction products through a directed modification of the protein environment in a controlled manner, is also discussed.

Keywords: Transfer, hydrogenation, imine, amine, reduction, asymmetric

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1 Introduction.

In recent years a significant amount of research has been carried out on the transfer hydrogenation of C=N bonds using complexes based on a range of metals but most frequently on the use of ruthenium, iridium and rhodium. Many of the advances have been in the use of asymmetric catalysts for this process, and several of these are closely related to similar catalysts for asymmetric hydrogenation using hydrogen gas as a reagent. In addition the combination of organometallic reagents with organocatalysts has been developed, as has the use of purely organocatalytic processes. A large number of synthetic applications, notably to pharmaceutical targets, have been reported.

The objective of this review is not to recount the early history of the transfer hydrogenation of C=N bonds, including asymmetric versions, because this has been reported adequately in a range of other reviews.[1-14] In addition, the mechanisms of the reactions have been discussed in detail. Hence whilst some recap is valuable in order to set the newer results into appropriate context, this review will focus primarily, although not exclusively, on newer developments in this area reported in the last 10 years, i.e. since and including 2005. There will also be a focus on the *applications* of C=N reduction which have been reported and the development of *asymmetric* methods and catalysts for this process. These will be distinguished by abbreviations for transfer hydrogenation (TH) and asymmetric transfer hydrogenation (ATH). The reducing agents (hydrogen sources) in the great majority of cases are either an alcohol (normally isopropanol –IPA – which is also used as the solvent), a combination of formic acid and trimethylamine (FA/TEA – usually used as a 5:2 azeotrope) or an aqueous solution of sodium formate (SF). The review will not cover hydrosilylation reactions, although some excellent reports have appeared in this area.[15-17] Organocatalysis, not involving a metal catalyst, is covered elsewhere in the volume and therefore not featured here although some reviews that have been published on this are highlighted for context.[18,19]

2 Organometallic catalysts for the transfer hydrogenation of imines.

2.1 TsDPEN /Ru and related organometallic catalysts.

Chemical methods for the TH of C=N bonds and notably the reduction of imines to amines have been known for many decades, early examples being the use of ruthenium complex $\text{Ru}_3(\text{CO})_{12}$ [20] and $[\text{RuCl}_2(\text{PPh}_3)]$. [21] In both cases, IPA was used as the reducing agent and a base was used to activate the catalyst. Relevant to the latter example, it was later demonstrated that $[\text{RuH}_2(\text{PPh}_3)]$ is an active TH catalyst which did not require added base.[22,23]

One of the most significant developments in imine ATH was reported in the mid-1990s when Noyori *et al.* reported their results on the use of the now very well established ruthenium complexes **1** of monotosylated 1,2-diamines in the asymmetric reduction of imines (Figure 1).[24] This important paper contained the first report of the application of this highly practical asymmetric catalyst for imine ATH. Of the series of catalysts tested, *trans*-1,2-diphenylethane-1,2-diamine (DPEN) formed the basis of the ligands, which could be created by converting just one of the amine groups to a sulphonamide- with a range of sulphonamides proving to be compatible. Of these, the monotosylated derivative (TsDPEN) is now probably the most widely used in the field. There is also some scope for variation of the η^6 -arene ring and its selection can significantly influence the activity and selectivity of the reductions.

Although a range of C=N bond-containing substrates were described, Noyori *et al.*'s study revealed cyclic imines such as dihydroisoquinolines (DHIQs) and dihydro- β -carboline (DHBs) to be excellent substrates. The reducing agent in this case was FA/TEA and an organic co-solvent was required. This paper contained an account of the application of the methodology to the synthesis of precursors of the Merck drug MK-0417. The reduction of acyclic substrates reported at this time proceeded in lower enantioselectivity however (Figure 1; note that the general reaction outcome using the (*R,R*)-configuration catalyst is illustrated, examples were given of the use of both catalyst enantiomers).

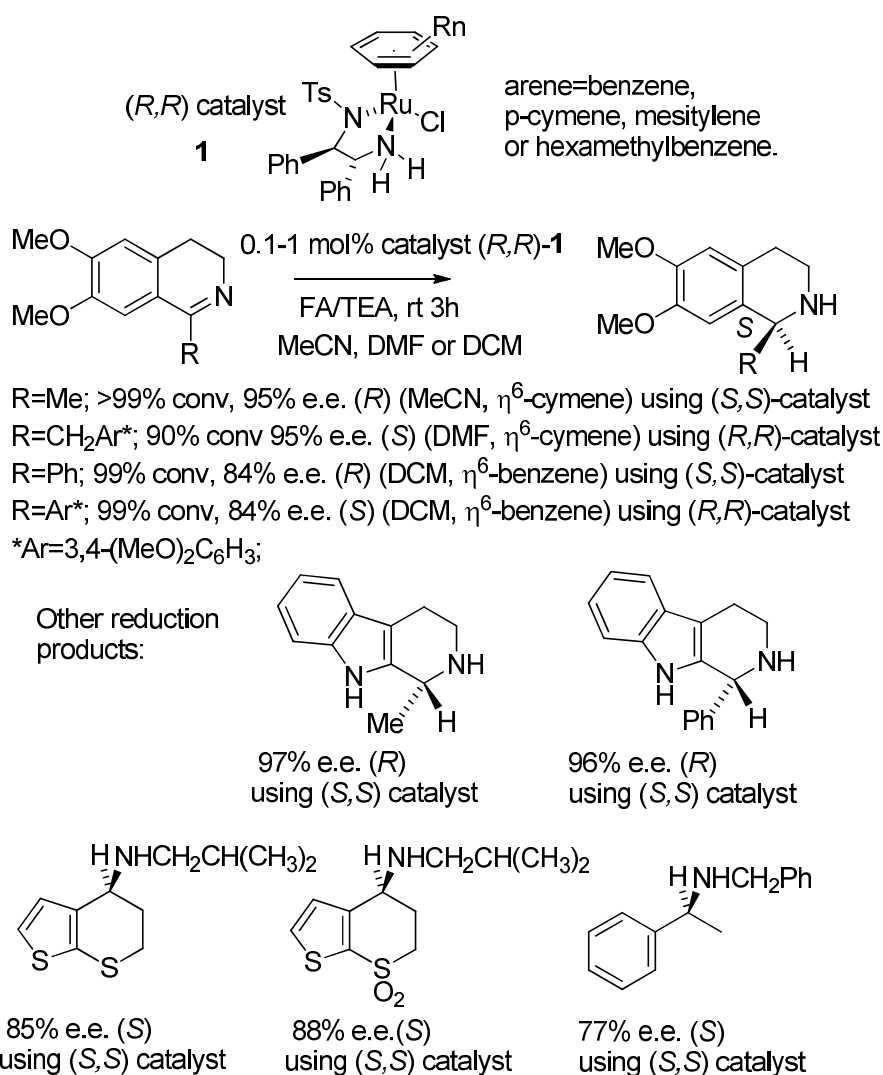


Figure 1

This initial result generated a great deal of future work in this area; many examples of applications of related reductions of substrates containing C=N bonds have since been reported and will be described later.

Closely related catalysts containing TsDPEN and related ligands with alternative metals – most significantly rhodium (III) and iridium (III) – have also been developed. In these examples, an η⁵-pentamethylcyclopentadienyl(Cp') replaces the η⁶-arene in order to maintain an isoelectronic structure. Although Rh(III) complexes of TsDPEN were first used in the ATH of ketones, Baker reported, in 1999, the use of complex **2** in imine reduction. In the majority of cases the selectivities were high, although some differences to the Ru(II) catalysts were also observed; for example the reduction of aromatic-substituted (as opposed to alkyl-substituted) and acyclic imines gave products of very low ee (Figure 2).[25] The commercialisation of the

Rh(III) derivatives was undertaken by a team at Avecia, who developed optimised approaches to a range of reductions of phosphinoyl-substituted imines, described in a later section.[26]

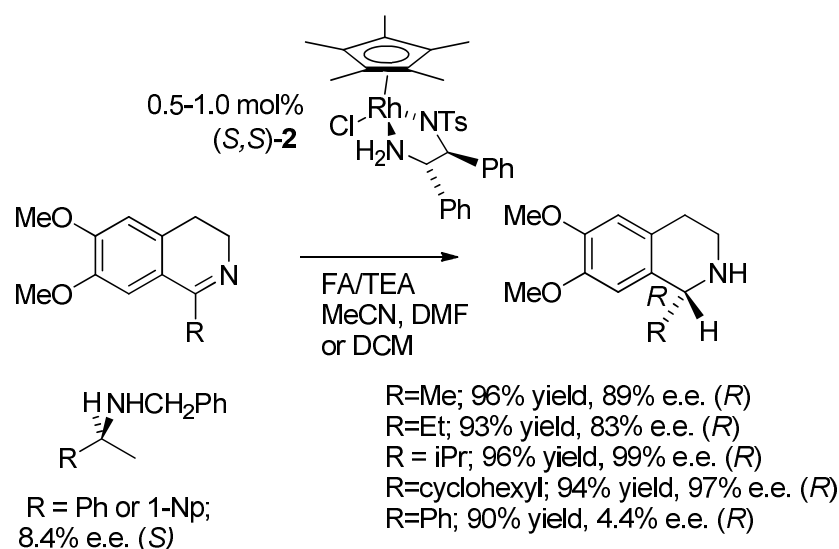


Figure 2

Progress has been made towards an understanding of the mechanism of reduction of imines using Ru(II) complexes of TsDPEN and a number of kinetic studies have been carried out.[27,28] Bäckwall *et al.* demonstrated that the protonated imine was required for reduction, by using the stoichiometric hydride reagent for the reduction [29]; whilst the iminium salt of a cyclic imine was reduced by this hydride, the unprotonated imine was not.

N-Alkylated derivatives of the catalysts, i.e. **3a-3f** also work well in the reductions of imines, provided that benzene is used as the η^6 -ring on the Ru(II).[30] In these studies the imine substrates were reduced within hours whilst the ketones required one or more days. Interestingly the N-methylated complex **3a** was slightly more active than the ‘parent’ complex **1** (Figure 3),[31] whilst the more hindered complexes were less active. In all cases the same product enantiomer was formed from each ketone and imine substrate irrespective of the catalyst used, suggesting a common mechanism between all the complexes. However it is noteworthy that the hydride is delivered to a different relative substrate face for the ketone ((*R,R*)-catalysts give *R*-configuration alcohol) compared to the imine ((*R,R*)-catalysts give (*S*)-configuration alcohol) The requirement for a stabilising H-bond between the NH of the ligand and the O atom of the ketone C=O group during the reduction of ketones is now well-established (Figure 4). It would appear that a single alkyl group on the N atom of the ligand within the catalyst does not hinder this interaction.[32]

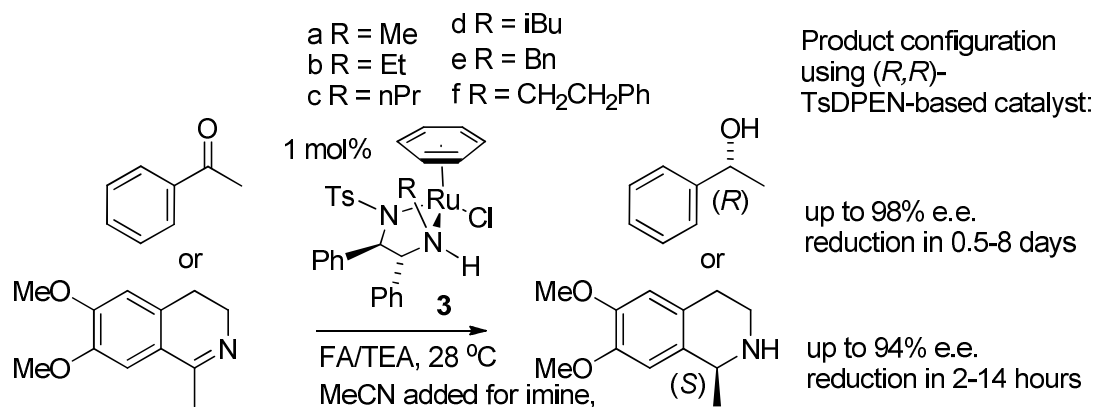


Figure 3

Wills *et al.* subsequently demonstrated that catalyst **4**, derived from a modified TsDPEN containing a dimethylated amine, was competent in the reduction of imines but not of ketones. The same was the case with the N-methylated ‘tethered’ complex **5**.^[33] This result provided evidence that the frequently-cited cyclic N-H hydrogen bond to the ketone which is essential for its reduction,^[34] is *not essential* in the case of imine reduction (Figure 4). On the basis of these results, it was proposed that imine reduction by Ru(II)/TsDPEN complexes proceeds through an ‘open’ (i.e. non-cyclic) transition state (Figure 4), which would account for the major product enantiomer observed whilst permitting the established edge/face stabilising interaction to operate between the H atoms on the η^6 -arene ring of the catalyst and the aromatic ring of the substrate.^[3,4] This would be analogous to observations previously reported on certain hydrogenation reactions of imines, where an ionic hydrogen transfer is proposed.^[35-37]

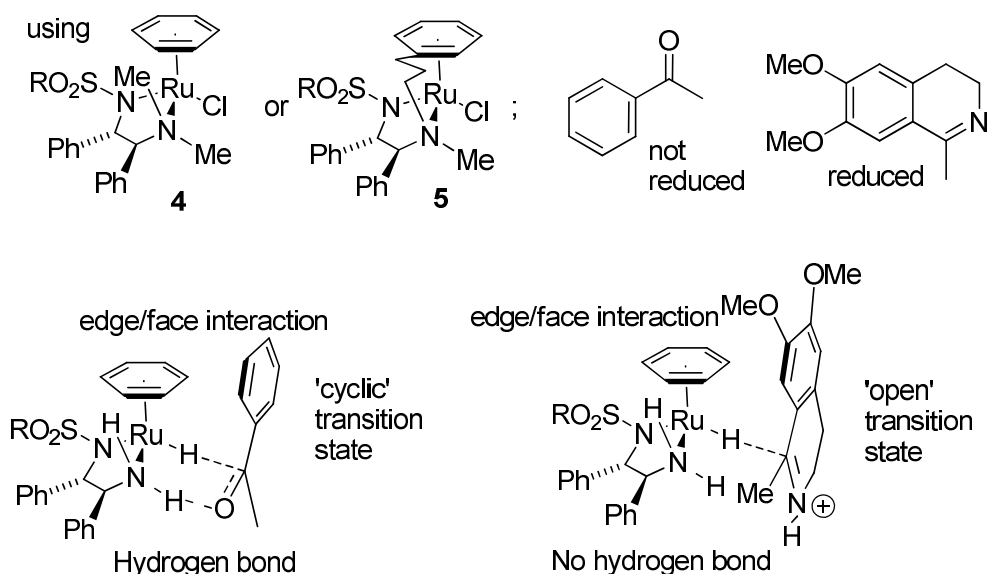


Figure 4

A series of reductions of imines to tetrahydroisoquinoline and tetrahydro- β -carboline alkaloids in aqueous media was reported by Pihko *et al.*[38] In this work, the addition of lanthanide salts resulted in improved selectivity and activity in the reductions, and the authors also proposed an ‘open’ transition state for the hydrogen transfer– in this case aided by the lanthanide as a co-catalyst (Figure 5).

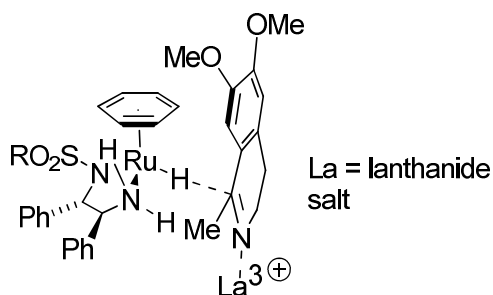


Figure 5

Subsequent molecular modelling studies by Václavík, Šot, Kuzma *et al.* also provided support for an ionic pathway for the reduction of protonated imines but with an additional stabilising interaction in the form of a hydrogen bond from the N-H bond from the substrate to the SO₂ group – serving to improve the direction and control of the reaction (Figure 6).[39,40]

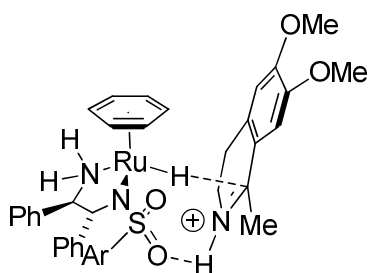
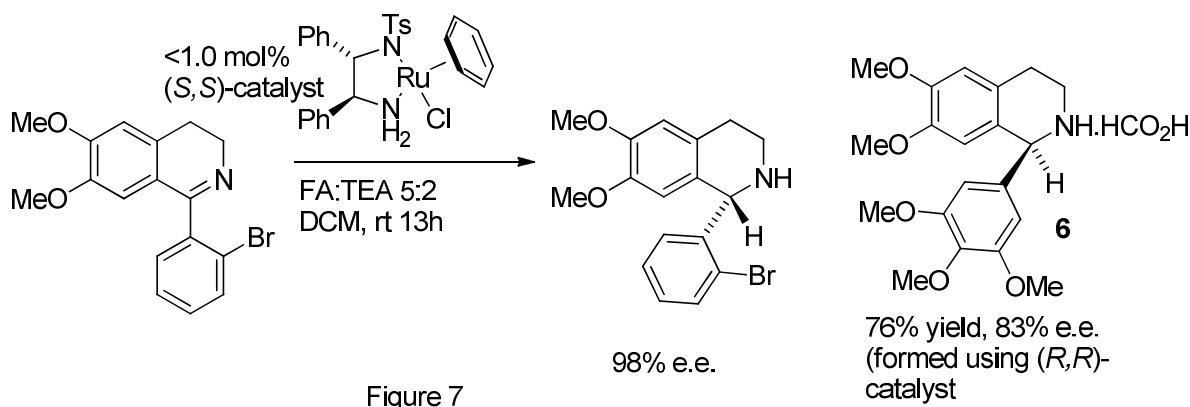


Figure 6

A detailed study by the same group, using by NMR, FTICR MS and vibrational circular dichroism, demonstrated that the use of different bases in place of the commonly-used triethylamine influenced significantly the activity and selectivity of imine reductions. A key finding was that the protonated base appears to interact with the hydride form of the catalyst during the reduction, probably via a hydrogen bond to the SO₂ unit – in addition to the other predicted interactions of the protonated substrate.[41,12] Hence the selection of base can have a significant moderating effect. In further computational studies on a related catalyst for ketone and imine reduction, it was demonstrated that the iminium cation reacts more quickly than the imine. A good catalyst for transfer hydrogenation is concluded to be one which ‘combines an electrophilic metal centre and a nucleophilic NH group’.[42,43]

2.2 Synthetic applications of Ru/TsDPEN and related catalysts.

ATH of dihydroisoquinolines was reported initially by Noyori and an early observation was that the reaction was lower enantioselective for substrates containing a 1-aryl group. Vedejs *et al.* reported several improvements to the reduction of these substrates (Figure 7).[44] Significantly, this group found that the *ortho*-bromophenyl substrate gave the best result (up to 98.7% e.e.) of a series of substrates tested in this application. A valuable example of an application was the asymmetric synthesis of (S)-(-)-cryptosyline **6** which was formed in 83% e.e. upon ATH. The e.e. could however be raised to >99% through subsequent recrystallization.[45] This was a key step of a total synthesis of the neuromuscular blocking agent GW0430.



In a further recent example of Ru(II)/TsDPEN-catalysed ATH of 1-aryl-substituted dihydroisoquinolines, a wide range of substrates were reduced using FA/TEA and iPrOH as solvent, with 1% catalyst. This series included challenging substrates with *ortho*-substituted aromatic rings.[46] In another report, 1-aryl substituted dihydroisoquinolines were demonstrated to be reduced in improved selectivity using a catalyst based on a borneolsulfonyl derivative of DPEN, compared to the more widely used TsDPEN.[47]

Significantly more reports have been published on the use of dihydroisoquinoline reduction where the 1-substituent is either an alkyl or a benzyl group, for which the enantioselectivity is generally high. Reductions of this class of substrate have led to many valuable breakthroughs. In many cases, the reducing agent is FA/TEA (5:2 azeotrope); one of the earliest was the report by Sheldon *et al.* giving products (intermediates in the synthesis of a series of alkaloids) in up to 99% e.e..[48] Likewise, Boros *et al.* used an ATH with FA/TEA as reductant catalysed by a Ru(II)/TsDPEN catalyst for the synthesis of intermediate **7** which is itself a component of a more complex product containing two tetrahydroisoquinoline rings.[49] Another example is the synthesis of emetines by Tietze *et al.* (Intermediate **8**) [50] and by Itoh *et al.* of the synthesis of **9**. [51] Many functional groups can tolerate the use of FA/TEA in the ATH reactions, including esters [52] and phthalimides.[53]

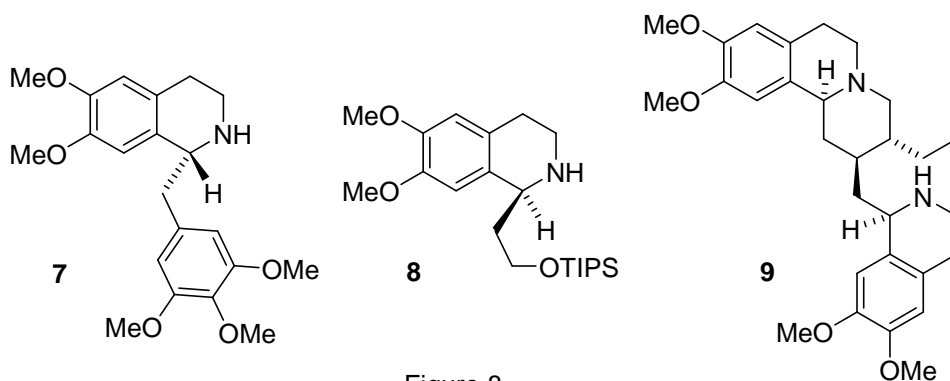


Figure 8

In an excellent examples of the industrial application of this methodology, a useful comparison was made between asymmetric hydrogenation (i.e. with hydrogen gas –AH) and ATH approaches to almorexant (ACT-078573A), a dual orexin receptor antagonist variant using a Ru/TsDPEN catalyst scaled up to 100s of kg of substrate. This specific targeted application worked very well under carefully optimised conditions, particularly when the methanesulfonate salt of the substrate was used. The use of a 1:1 ratio of FA:TEA gave a more rapid reaction compared to the more-widely used 5:2 ratio, and the formation of a small amount of the formylated side product was observed but this was minimised during the process optimisation (Figure 9).[54] Following a recrystallization, 87% of product was isolated in 99.7% e.e. on a 18 kg scale which required 17g of catalyst.

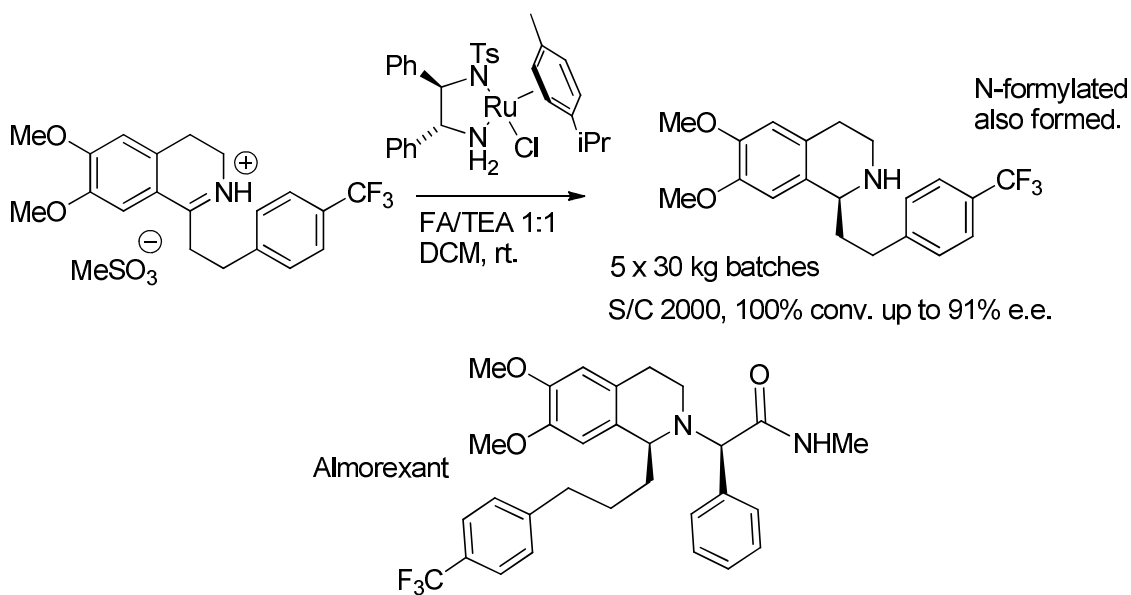


Figure 9

In another excellent example of an application, the enantioselective total synthesis of (-)-(*S*)-stepholidine, a candidate for treatment of schizophrenia, was achieved through a C=N reduction, in >99% e.e. and 42% yield (Figure 10).[55]

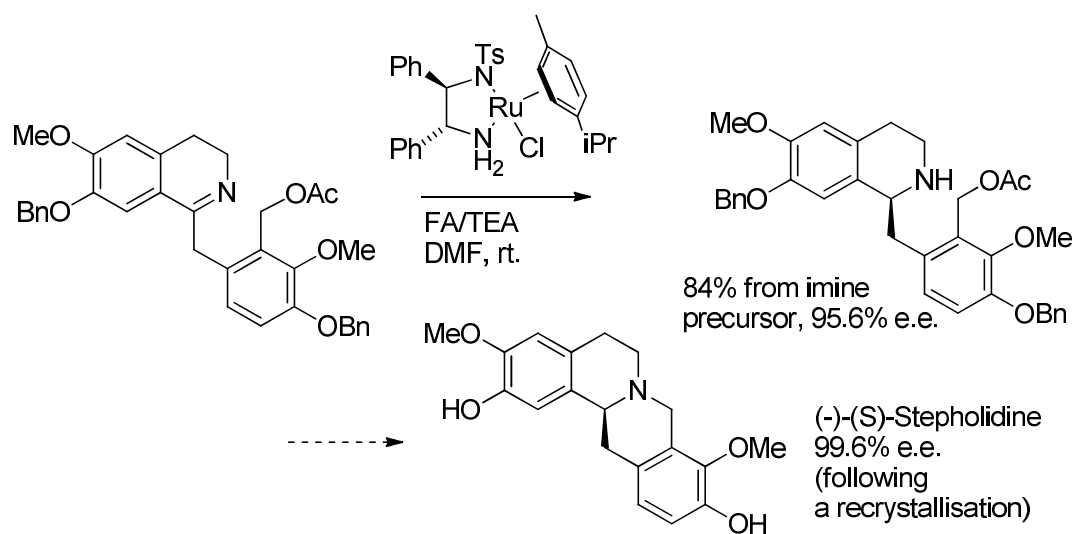


Figure 10

Reductions of imines can also be carried out under aqueous conditions; the aqueous process appears to be readily applicable to dihydroisoquinoline reduction and also for dihydro- β -carbolines (discussed in more detail later) but can be significantly enhanced by the addition of a silver salt and $\text{Ln}(\text{OTf})_3$ or a closely related salt (Sc, Y, Ce, Yb, Bi salts were tested) and therefore applied to more challenging substrates than would otherwise be possible (Figure 11).[38] The use of a combined methanol/water solvent also provides some advantages in the most difficult cases. The acceleration of the reduction through an ‘open-TS’ hydride transfer mechanism using a lanthanide cation as a Lewis acid has been described above (Figure 5).

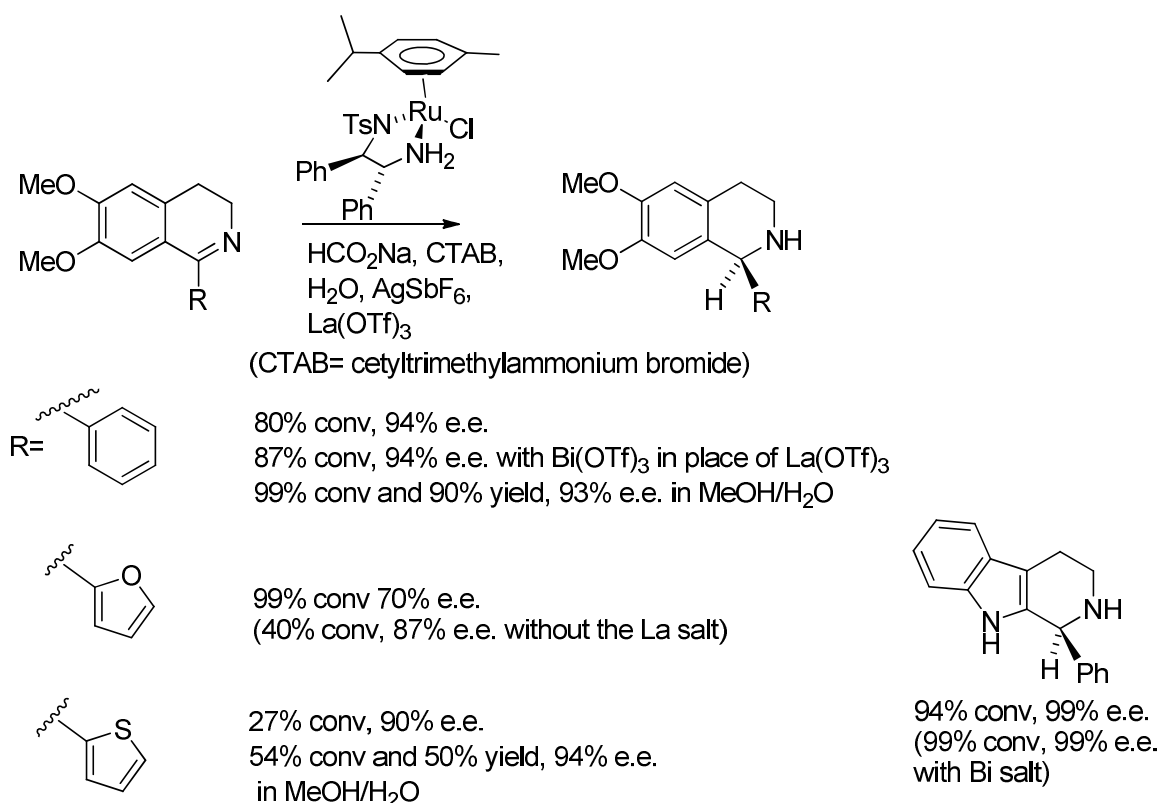
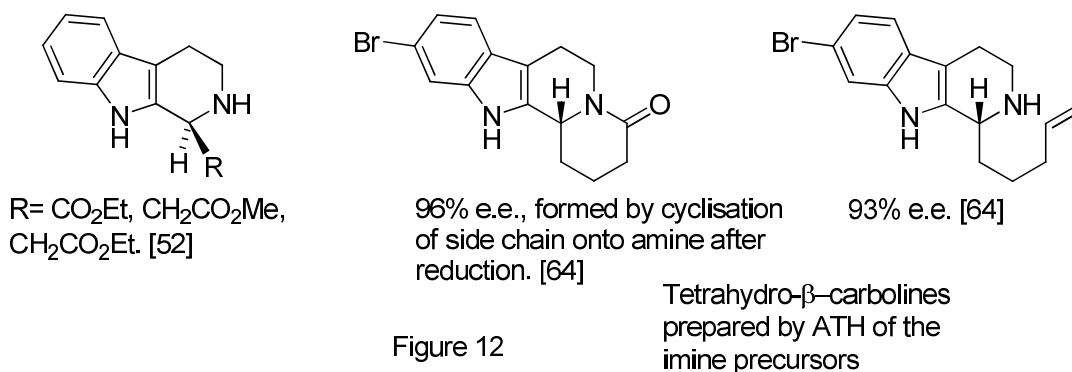


Figure 11

In a comparative study, two optimized approaches to mivacurium chloride (and other skeletal muscle relaxants) was reported. (*R*)-5'-Methoxylaudanosine was prepared by ATH of a dihydroisoquinoline and the process was compared to a resolution strategy.[56]

Several studies on the various parameters which influence the ATH of DHIQs have been reported,[57,58] and reductions have been monitored by NMR spectroscopy in order to generate valuable kinetic data.[59,60] A study of five substrates revealed that rate and e.e. are substrate dependent[61], whilst the effect of the η^6 -aromatic ring revealed that hexamethylbenzene series is very slow; two DHIQ substrates were investigated.[62] The ATH of imines (and ketones) using tethered Rh(III) catalysts has also been reported.[63]

Cyclic dihydro- β -carboline, originally exemplified by Noyori,[24] are another class of substrate popular for ATH reactions, since their reduction products are represented in biologically active targets. Examples of targets which can be prepared through reduction in the popular FA/TEA system (often together with a cosolvent) are illustrated in Figure 12. [52,64]



Iminium salts can likewise be used as excellent substrates for ATH reactions. Czarnocki *et al*, have completed a short synthesis of (*R*)-(+)-crispine A **10** through the reduction of the iminium salt **11**, [65,66] and this has been extended to further iminium substrates (Figure 13) which have been successfully reduced. [67] The compounds could be purified to enantiomeric purity using a recrystallisation after the reduction.

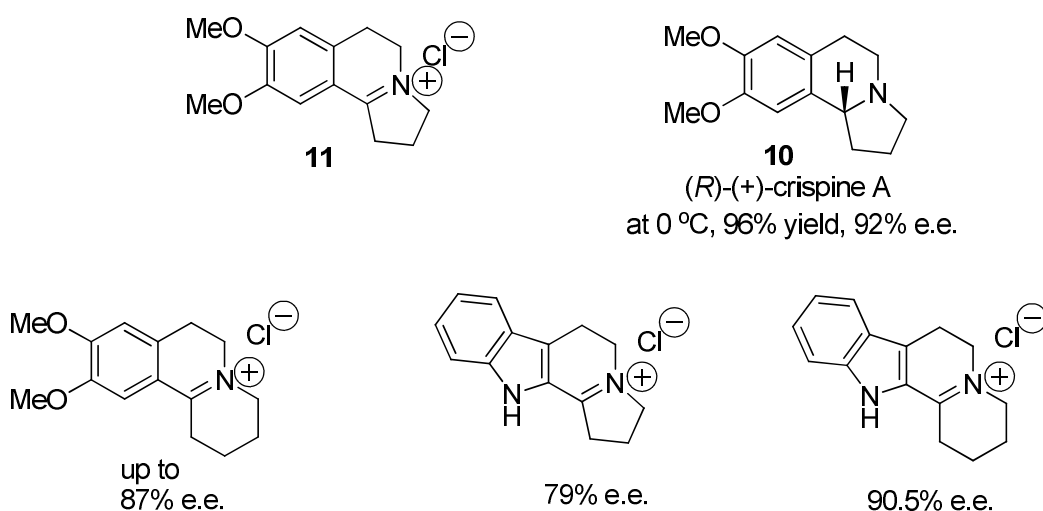


Figure 13

The use of a Ru(II) catalyst containing a proline-derived tetrazole ligand has been reported in a synthetic application; the reduction of an iminium cation en route to (*S*)-(-)-lennoxamine (Figure 14). The study provided an interesting contrast between the use of both ATH and AH reduction methods, the selection depending on the metal used. [68]

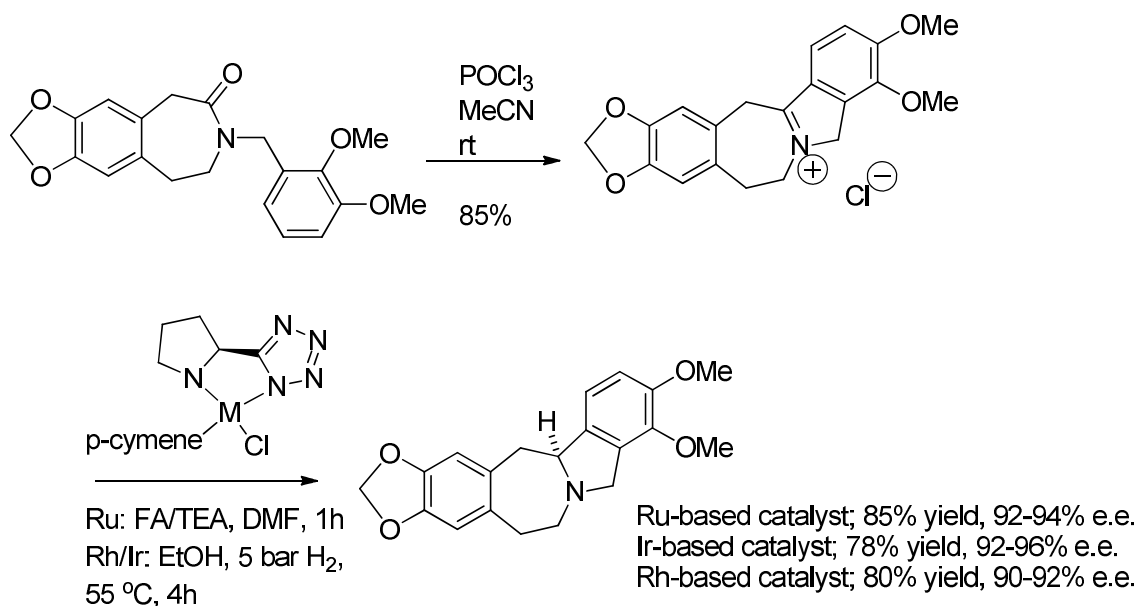


Figure 14

In addition, the synthesis of new mono-N-tosylated diamine ligands based on (*R*)-(+)-limonene and their application to ATH of cyclic imines and iminium salts gave good results; up to 98% e.e. in some cases.[69] Reductions of iminium salts using 1.2 mol% of a Ru(II) catalyst, using sodium formate with cetyltrimethylammonium bromide (CTAB) in aqueous solution, with the addition of silver hexamethylantimonate, have been described.[38]

ATH can be used to form sultams (Figure 15) in a very efficient and selective reduction using Ru complexes [70] and indeed this was one of the first reported applications of the Ru(II)/arene/TsDPEN complexes. Analogous Rh(III) complexes can also be used.[25]

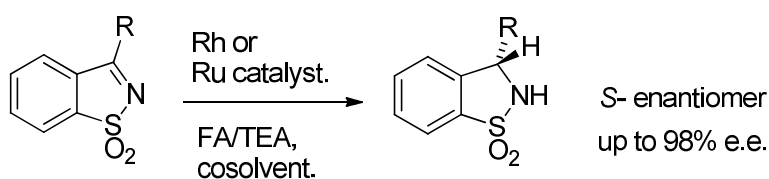


Figure 15

Dendrimer and polymer-supported catalysts can be employed in the ATH of sultam precursors,[71,72] including examples where the supporting material has sulfonyl groups and therefore assists reactions in water.[73] The synthesis of an amphiphilic polystyrene-type immobilised TsDPEN ligand and its application in ATH of cyclic sulfonimines has been reported (Figure 16).[74]

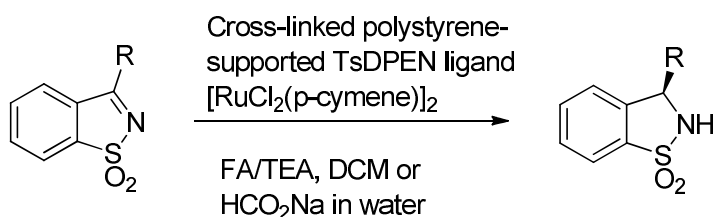


Figure 16

Acyclic N-sulphonylated imines can also be reduced by ATH although selectivities are lower.[72]

Other polymer-supported systems for C=N ATH feature polymer microspheres functionalized with a chiral ligand by precipitation polymerization[75] and the use of recyclable organoruthenium-functionalized mesoporous silica; reduction of quinolines in up to 99% e.e. was reported.[76] The efficient ATH of N-sulfonylimines on water using a Rh-imido complex preceeded with higher reactivity and enantioselectivity compared to the homogeneous reaction. Interestingly, the reactivity appears to depend on stirring speed of the reaction as well as other experimental factors.[77] The ATH of imines and ketones under aqueous conditions has been reviewed in detail.[78,79]

As well as the more established TsDPEN ligand derivatives, proline-derived, water soluble arene Ru(II) catalysts containing sulfonylated ligands have been used for ATH of α -aryl ketones and imines in aqueous solution.[80] The ligands in Figure 17 were prepared and incorporated into Ru(II) aqua complexes (i.e. cationic) – the effect of the pH in aqueous reductions was also studied and was optimal at about 8-9 with these catalysts.

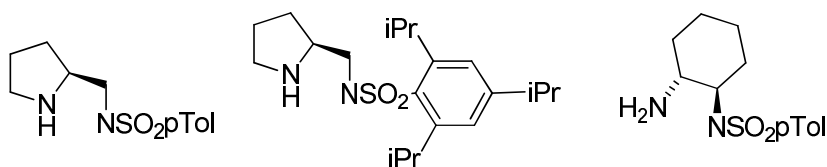


Figure 17

Another example of the reduction of ketones and imines with a novel water-soluble chiral diamine **12** as the ligand in neat water has been reported (Figure 18).[81] Cyclic imines were reduced in high e.e.

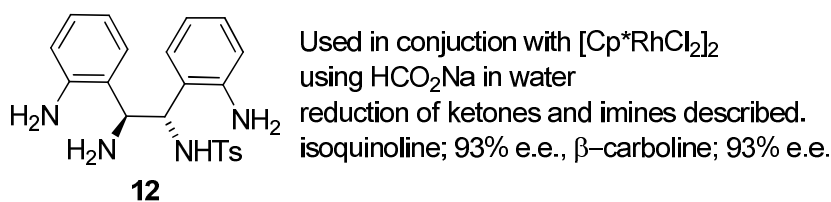


Figure 18

The combination of methanol and water gives improved results in some cases.[38] The use of Rh/TsDPEN catalysts on cyclic imine in a mixture of MeOH and water gives the highest rates e.g. reduction in 20 min for 98% conversion, whereas water or MeOH alone takes at least 300 minutes for similar conversion.[82] In a detailed paper on the use of crosslinked polystyrene, the polymer supported reagents can reduce benzyl amines, in FA/TEA/DCM in up to 93% yield; Ru(II) catalysts gave the best ees. An amphiphilic version containing some sulfonic acid groups in water with sodium formate also reduced cyclic imine in good efficiency.[83]

Further examples of supported catalysts used for ATH of imines include those based on recyclable silica,[84] functionalised MCM-41,[85] siliceous mesocellular foam[86] and magnetic mesoporous silica. In the latter case the reusable immobilized catalyst exhibited high activity and enantioselectivities in the ATH of imines in FA/TEA. It could be separated mechanically using an external magnet to facilitate ready recycling.[87]

The enantioselective synthesis of α -trifluoromethyl arylmethanamines by Ru(II)/aminoindanol ATH is very efficient and gives products in high yield and e.e. (Figure 19). Several ligands were used and tested and a good number of examples were reported, including an application to the synthesis of an analogue of a plant disease control agent.[88]

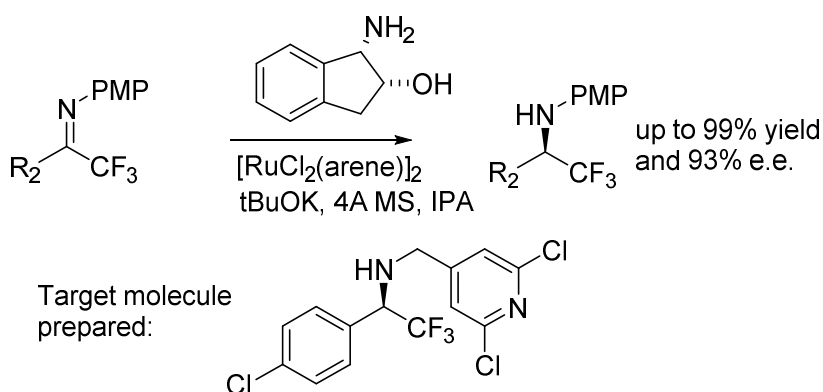


Figure 19

Ru(II)-catalysed ATH of α -trifluoromethylimines was also achieved using TsDPEN-based catalysts under aqueous conditions (Figure 20).[89]

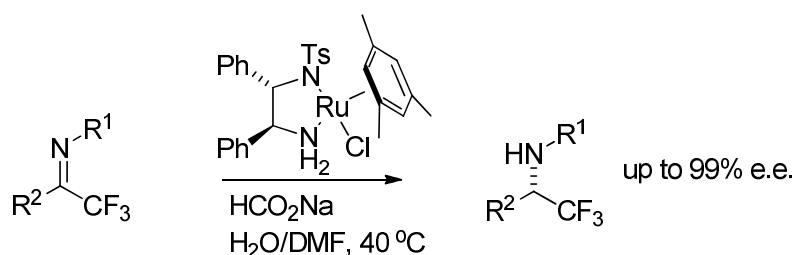


Figure 20

Several reports have recently appeared describing the ATH reduction of cyclic sulfamidates and sulfamides, following the report of this in 2010.[90] The synthetic routes to key substrates and their reductions by Rh(III) catalysts are shown in Figure 21. In all cases the ees of the reductions were excellent, and the reduction forms the basis of an efficient synthesis of enantiomerically enriched 1,2-aminoalcohols and diamines.[91]

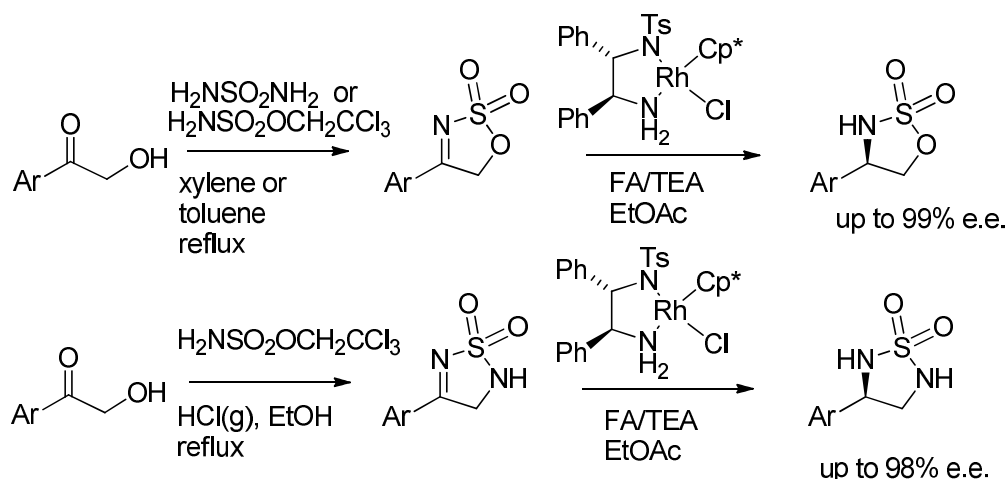


Figure 21

The reduction of this class of substrate can be extended to a dynamic kinetic resolution (DKR) process with C=N reduction coupled to racemisation of the adjacent stereocentre. Of the Ru, Rh and Ir catalysts tested, the Rh catalyst gave the best results (Figure 22). The resulting compounds could be converted into other products through S_N2 ring-opening using phosphorus and nitrogen nucleophiles. Typically the reductions exhibited a selectivity of $>20:1$ in favour of the *cis*- product, and ees were typically 94-97% but up to 99% e.e. in a number of cases. An exception was for more hindered *ortho*-substituted substrates e.g. $R^1=R^2=ortho\text{-ClC}_6\text{H}_4$ the e.e. was only 22%.[92]

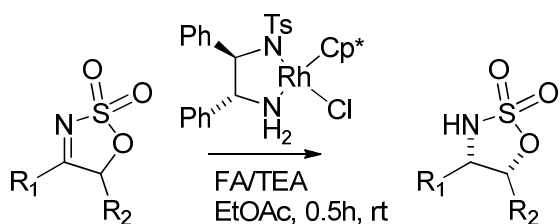


Figure 22

The stereoselective synthesis of 4-substituted cyclic sulfamate-5-carboxylates can be achieved using this process of coupled ATH/DKR (Figure 23) and this method has been applied to the synthesis of (-)-*epi*-cytoxazone and the taxotere side-chain. The *cis*- isomer was formed in high selectivity; typically >25:1. A wide range of examples were reported, with 3 and 4-substituted aromatic groups, the ees were up to 99% in many cases and generally >95% e.e. An example with cyclohexyl was less selective (Figure 23).[93]

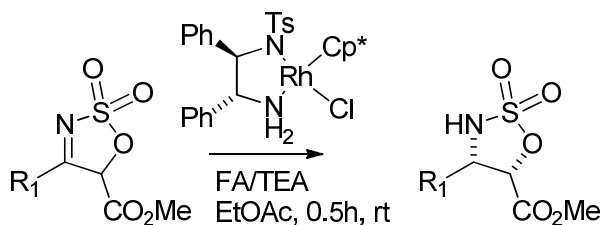


Figure 23

The application could be extended efficiently to 5-phosphonate-containing substrates. In some cases both the de and e.e. were >99% (Figure 24).[94]

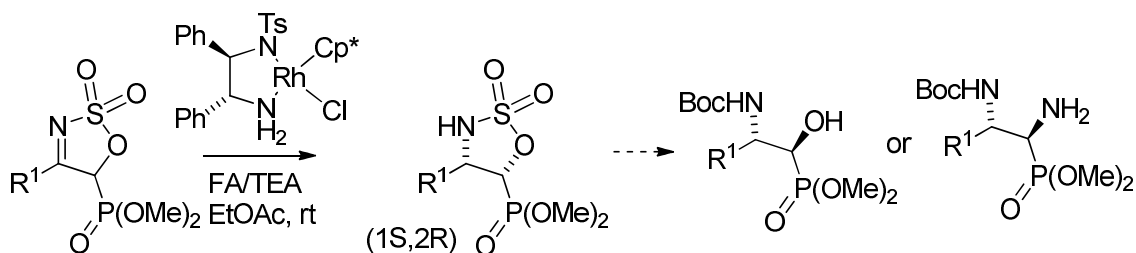


Figure 24

Related work on the reduction of two C=N bonds sequentially has been reported. In this case the Ru(II) catalyst was first used and gave good results. Preferential reduction of one C=N is observed but the other can be stereoselectively reduced using lithium borohydride; the products were transformed into chiral diamines (Figure 25).[95]

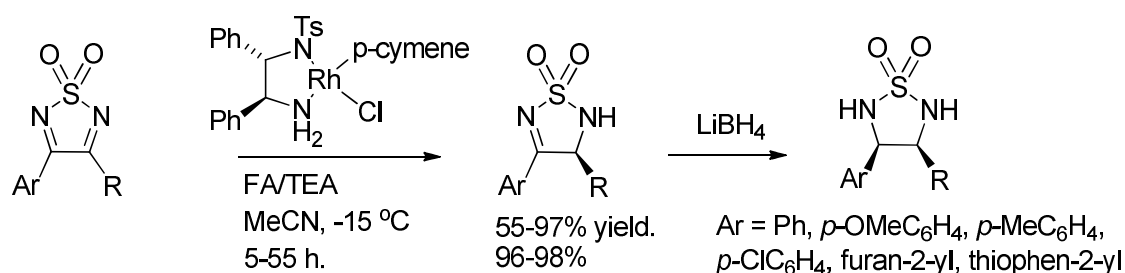


Figure 25

Asymmetric aziridines can be prepared by ATH of an azirine; this was one of the earliest reported applications of the use of Ru(II) complexes, achieved using a bicyclic amino alcohol ligand (Scheme 26).[96]

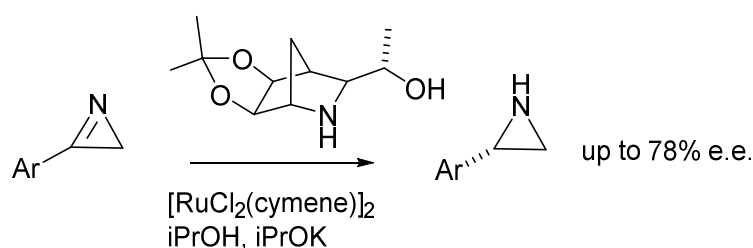


Figure 26

The application of Rh(III) systems to the reduction of N-phosphinoyl imines has been described in depth by researchers from Avecia, who were able to obtain some very valuable insights into the mechanism of the reaction and requirement for removal of carbon dioxide during the reaction.[26] In recent related work, Guijarro *et al.* described the use of chiral beta-amino alcohols as ligands for the Ru(II)-catalyzed ATH of phosphinyl ketimines. It was demonstrated that the reaction was possible using *cis*-amino indanol (CAI) as ligand for the catalyst. A number of amino alcohols were tested but CAI was the best of the series (Figure 27). Most of the studies were conducted on acetophenone-derived imine but in examples where Ar=Ph, R=Et gave a product of 82% e.e. and Ar=pClC₆H₄, R=Me gave one of 80% e.e.[97]

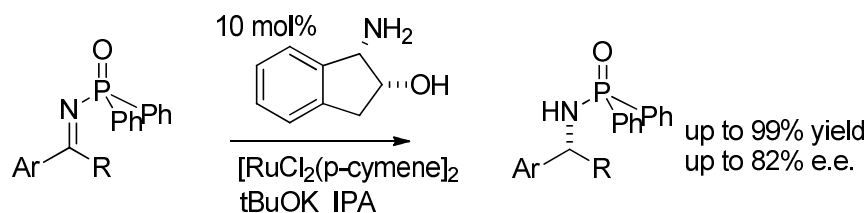


Figure 27

In early work, Lassaletta *et al.* described a DKR reaction coupled to the formation of primary amines.[98] In a related process, an efficient ATH reaction for the synthesis of an advanced intermediate to a drug for the treatment of human papillomavirus infections, has been reported (Figure 28). This involves an interesting *exo*- C=N reduction in an in-situ process. The formation of an imine followed by a reduction using a Ru(II)/BINAP complex was also investigated, as was a diastereoselective method using alpha-methylbenzylamine as a directing group.[99]

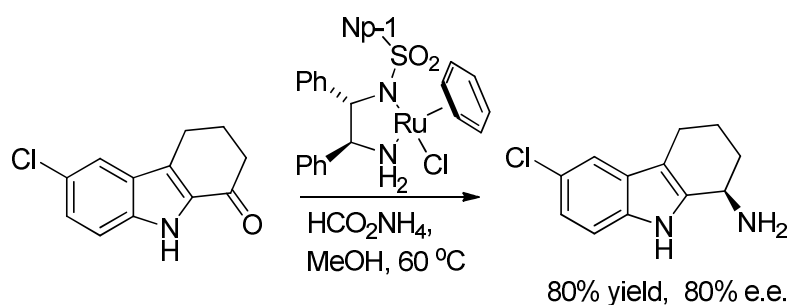


Figure 28

A similar reduction towards a primary amine intermediate was reported by scientists at Merck (Figure 29). The target in this case was the HCV NS5a inhibitor MK-8742, and a key step was a highly enantioselective ATH of a C=N bond. Of the catalysts investigated, the best one proved to be the tethered catalyst reported by Wills *et al.* The synthesis of the complex target requires simple starting materials and just nine linear steps for completion.[100]

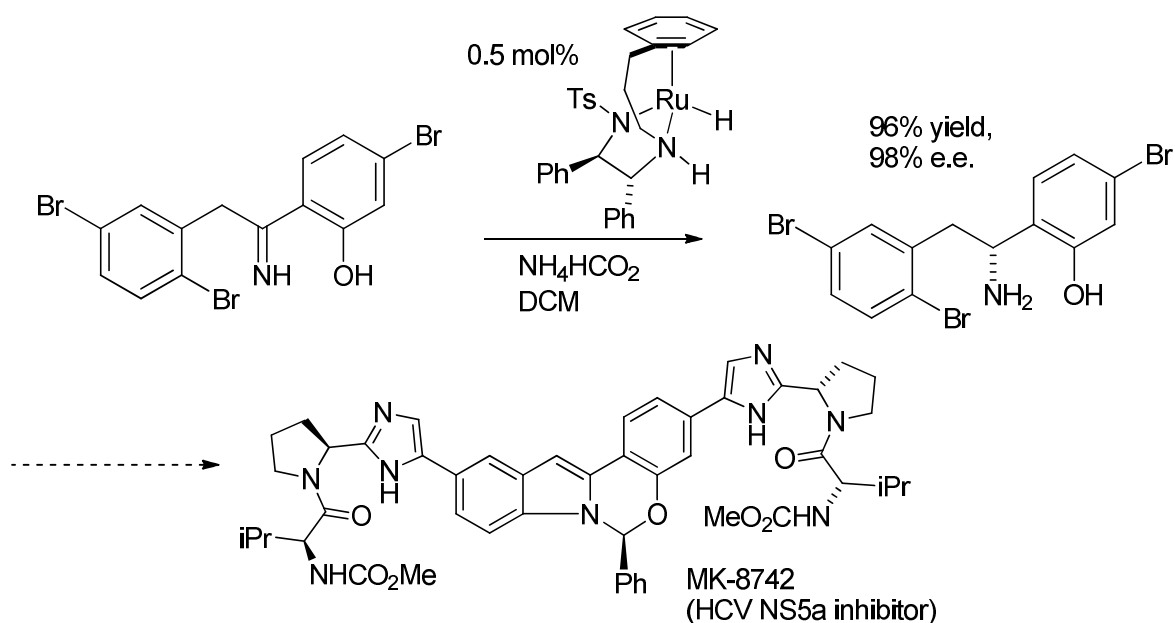


Figure 29

Also in earlier work, Wills *et al.* described the formation of C-N bonds in a one-pot ATH starting from Boc-protected amines.[101,102] This type of process was applied in an impressive intramolecular ATH reaction in a key step to the dual orexin inhibitor molecule Suvorexant (MK-4305) (Figure 30).[103] This excellent detailed paper on reductive amination employed Ru(II)/TsDPEN catalyst in the reductions, and the best results were obtained using a derivative containing a very hindered aromatic group on the sulphonamide unit. The operation of the ‘open’ transition state for hydride transfer to the imine is described. The paper contains details of extensive investigations into the effect of excess carbon dioxide on the reaction; purging this from the reaction gives better rates. The significance of the formation of two diastereoisomers of the hydride form of the catalyst, which has been previously observed for this type of catalyst, was also discussed in some depth.

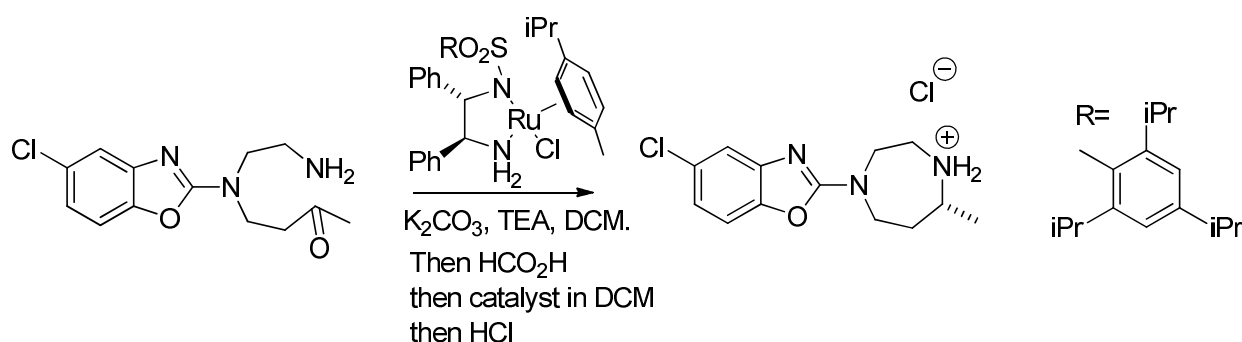


Figure 30

Heteroaromatic substrates have been productive targets for both TH and ATH reactions. Quinoline, and isoquinolium salts can be reduced by Ru(II) and Rh(III) catalysts by ATH.[104,105] Chemoselective reductions of quinolines were achieved by TH using IPA with an iridium catalyst (Figure 31).[106]

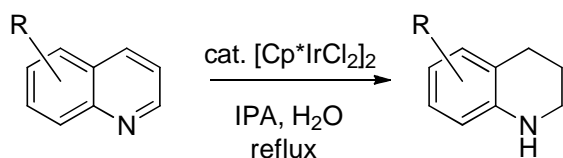


Figure 31

The importance of Ph-regulation for the TH of quinoxalines with a $\text{Cp}^*\text{Ir}/\text{TsEN}$ catalyst in water has been demonstrated; the reduction using HCO_2Na . at ca pH 5.5 (regulated with a

buffer) is shown to give the highest rates.[107] In another report, a dramatic effect of added iodide was shown to influence TH of a number of N-heterocycles (quinolines, isoquinolines and quinoxalines) when a Cp*Ir catalysts was employed for their reductions in FA/TEA.[108]

However some important asymmetric examples have been reported; again pH-regulation has been shown to be crucial to the successful ATH of quinolines in water with sodium formate as the reducing agent; the rate peaks at around pH 5.0 and formic acid with a formate buffer is used to regulate this. The best of a series of catalysts was a Cp*Rh complex of a p-(t-butyl)benzenesulfonylDPEN although other ligands were also viable. Reductions were complete typically within 6-24h at 40 °C using 1 mol% of catalyst (Figure 32).[109]

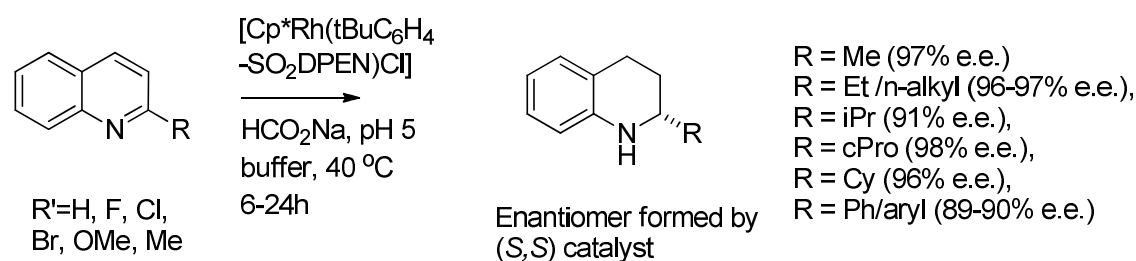


Figure 32

A similar process was reported using tethered Ru(II) catalysts (Figure 33).[110]

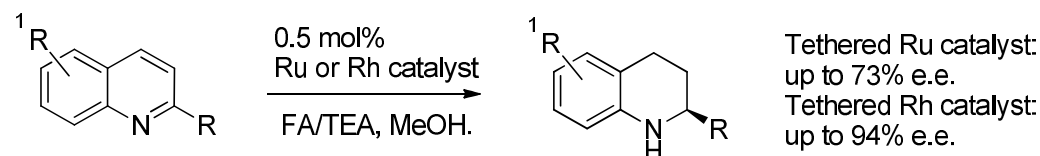


Figure 33

A mesoporous silica-supported TsDPEN/Ru(II) catalyst has also been applied productively to this transformation.[76]

2.3 Shvo-type catalysts and other classes of organometallic catalysts

The Shvo diruthenium catalyst **13** (Figure 34) has been used in non-asymmetric ketone and imine reduction, and the mechanism has been studied and reported in some detail.[111-115][5] Catalyst **13** is also able to racemise amines,[116] which allows it to be combined in a DKR process with an enzyme to create enantiomerically-enriched amides.

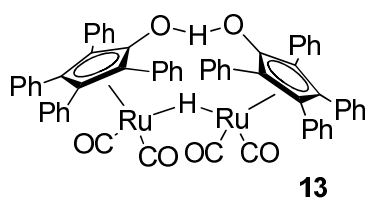
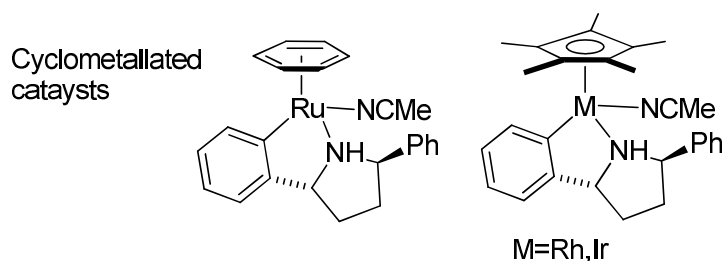


Figure 34

Iron cyclopentadienone complexes have recently emerged as alternatives to Ru(II) catalysts, although their main focus is on ketone reduction rather than imine reduction.[117]

Bifunctional rhenium complexes, related to the Shvo catalyst, have been used in TH reactions, including tests on three non-prochiral imines, TOFs up to 79 h^{-1} were obtained for imines. In common with the Shvo catalysts, DFT calculations indicated the operation of an outer-sphere mechanism for the reaction.[118]

Cyclometallated complexes of Ru, Rh, Ir have been used as ATH catalysts; Some examples of this class of catalyst have been prepared and reported earlier, however their applications have now been extended to a broader range of target imines, both cyclic and acyclic (Figure 35).[119]



Substrates reduced: (FA/TEA, DCM, [S]=0.016M, 1 mol% catalyst.

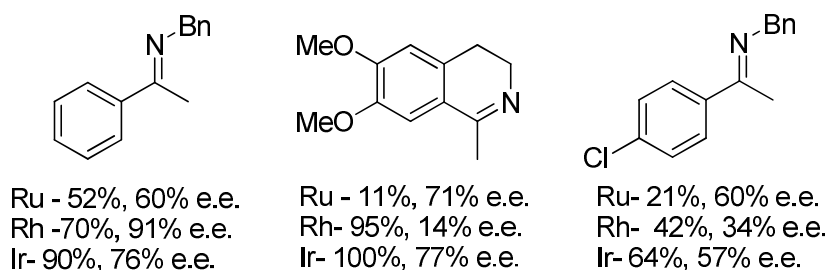


Figure 35

Ru-Pybox complexes have been used to achieve imine ATH in IPA; these complexes gave some excellent results for imine derivatives of acetophenone with products of up to 99% e.e. in some cases using 1 mol% of catalyst (Figure 36). There was some mechanistic discussion

and a number of examples were reported. In general these complexes have been used much more widely for ketone ATH.[120]

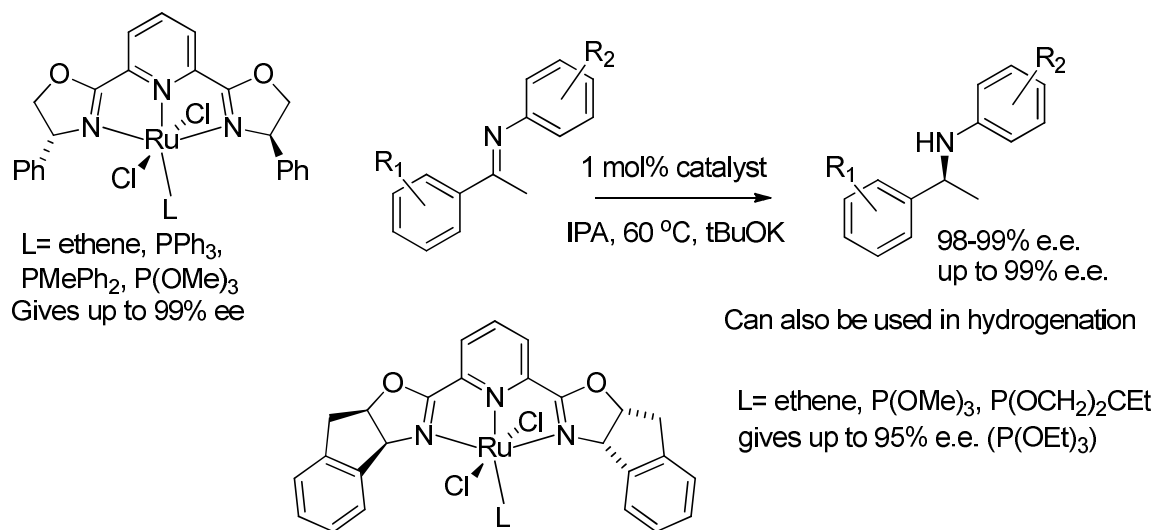


Figure 36

A very interesting report of a nickel-catalyzed ATH of hydrazones and related substrates has been published. Using a complex formed from a combination of (*S*)-binapine and a Ni(II) source, with FA/TEA as the reducing agent, products of up to 97% e.e. were formed in the reduction (Figure 37). The reaction also works with sultams, giving products in 98-99% e.e. Deuterium labelling studies were also carried out, in D-FA and during the reduction, resulting in deuteration of the Me group and indicating that exchange could be taking place through an enamine.[121]

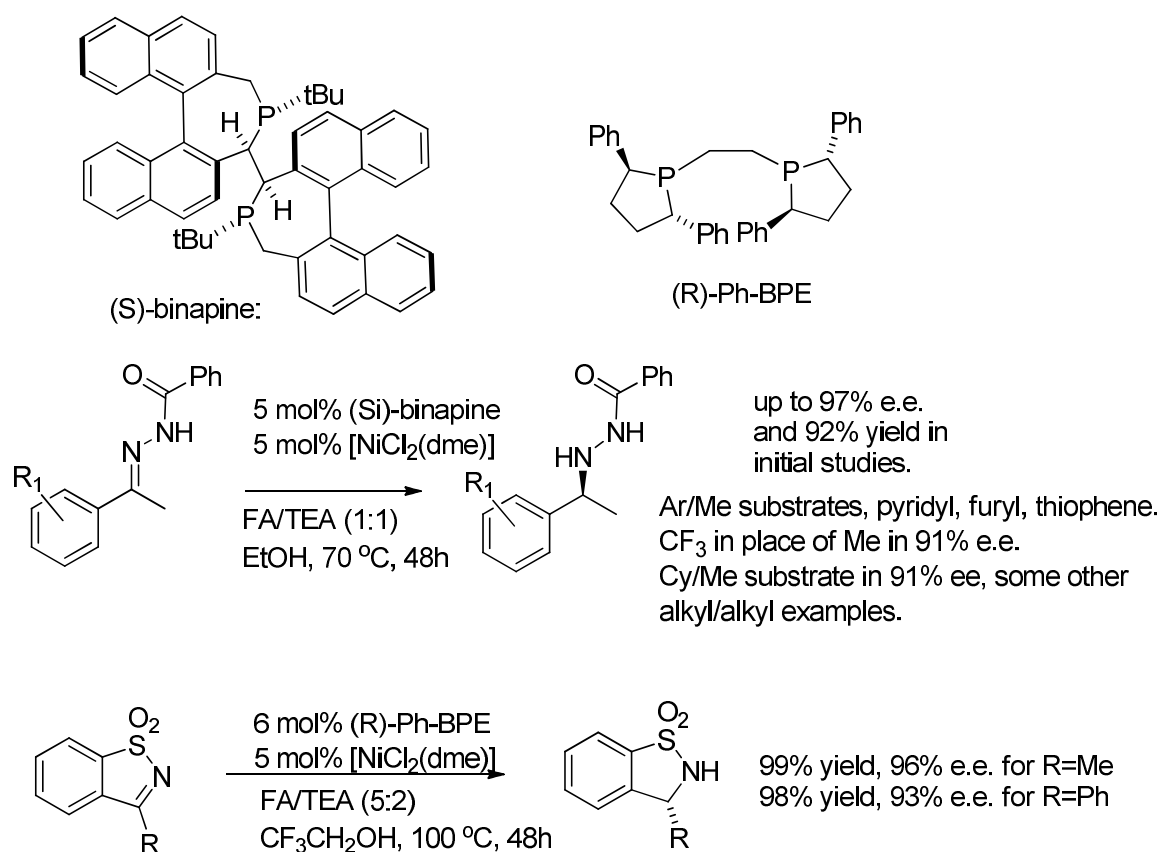
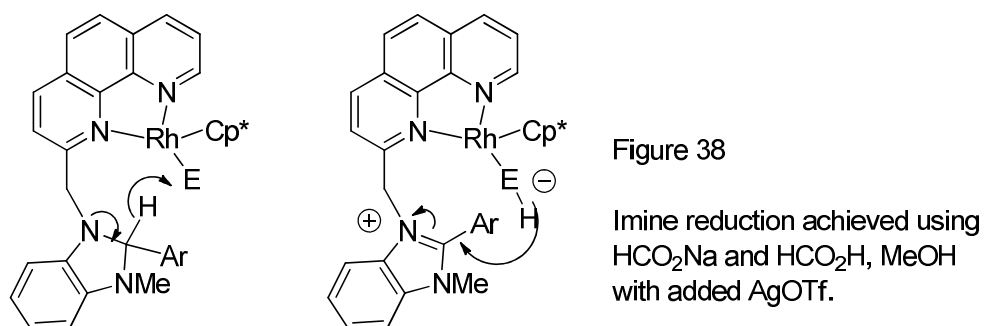


Figure 37

A bio-inspired catalyst comprised of a combined organic hydride donor with metal centre has been reported for TH of imines. A previously used catalyst relied on a Hantzsch ester but the newer derivative benefits from more readily preparation and greater accessibility. Yields are high for the Rh complex containing all the components and more than for the Ir complex or the complex containing the phenanthroline ligand alone (Figure 38).[122,123]



Several iron complexes for imine ATH have been developed by Morris *et al.* IPA is used in the reduction. Early examples of the PNNP-complexes (containing imine ligands) of iron gave

100% reduction of PhCH=NPh but only 5% of PhCMe=NPh.[124] Beller reported the use of an in situ-generated catalyst for ATH of imines with high yield and enantioselectivity (Figure 39).[125]

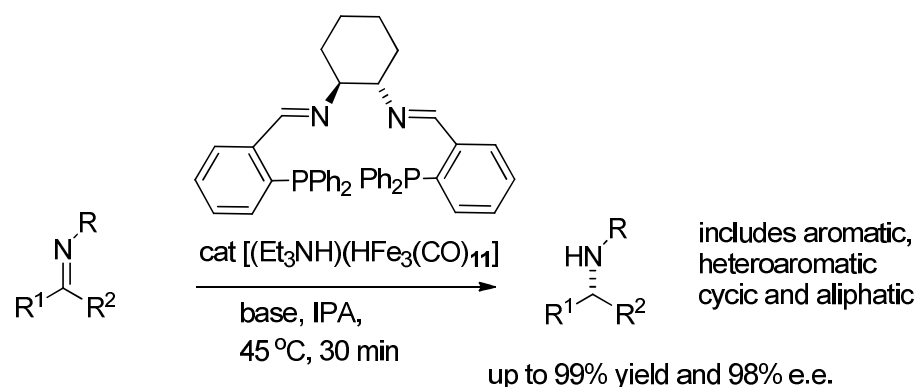


Figure 39

However Morris *et al.* later discovered that iron complexes containing a combination of one amine donor and one imine donor (e.g. **14**) were superior catalysts for ketone and imine ATH (Figure 40). The researchers followed on from results which indicated that the proposed reduction of one C=N bond of the original ligands was important to the mechanism. They prepared an amine/imine ‘P-NH-N-P’ ligand first by adding one C-NH bond in a reductive amination process and then forming the second, C=N bond and finally the ‘third generation’ complex **14** (Figure 40). This new class of catalyst was effective in the rapid reduction of N-diphenylphosphinoyl activated imines containing phosphinoyl groups in >99% e.e. (Figure 41).[126,127]

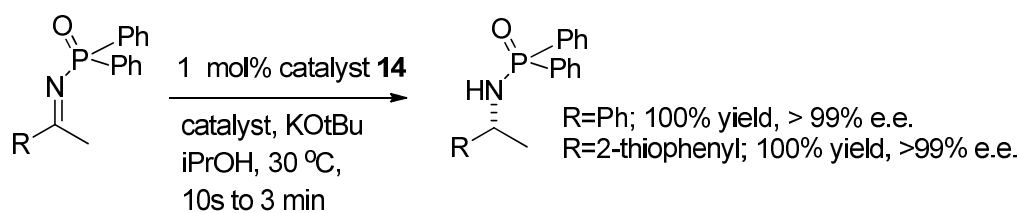
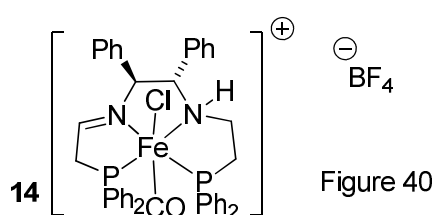


Figure 41

Full documented details of synthesis and use, including pictures of the reaction setup have been published.[128]

Very few examples of osmium-catalysed ATH reactions of imines have been reported.[129] However one example is provided by arene iminopyridine halido complexes which additionally exhibit properties as antitumor agents. Four complexes were prepared and tested, giving reductions in FA/TEA of ca. 22-23% e.e. in each case (Figure 42).[130]

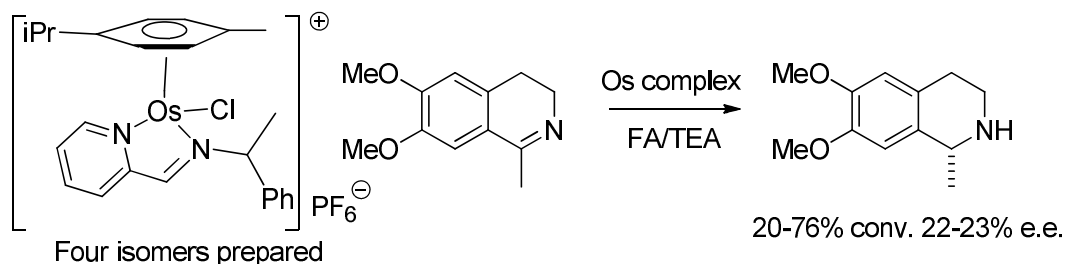


Figure 42

2.4 Incorporation of TH catalysts into proteins.

One of the significant developments within the decade leading up to this review have been the contributions made to the development of organometallic reagents contained within protein structures, relying on the asymmetric environment of the protein to generate asymmetry in the reductions when a simple (i.e. non-chiral) complex is added to it. Many contributions have been made by Prof T. Ward *et al.*, and principally through the attachment of an organometallic complex of a non-chiral Ts-diamine ligand to biotin, thus allowing it to be coordinated within the chiral environment of a streptavidin molecule and hence an asymmetric induction generated. Important to this process is the ability to modify the streptavidin structure in a selective manner in order to optimise the reactions towards these substrates. This section shall examine the principle developments in this area, which is a part of a larger programme on many applications of metal/protein complexes.

Following extensive work on optimising the catalysts towards the reduction of ketones, studies were extended to imine reductions. The illustration in Figure 43 illustrates how a component of the protein (i.e. a lysine side chain) can stabilise the iminium substrate during the reduction by an iridium catalyst which is chiral at the metal and within the chiral environment created by the protein. In common with other models previously described for imine ATH, the ‘open’ transition state for the reduction is proposed. This is based on observed results and X-ray crystallographic evidence; the S112A variant containing the Ir/TsEN (EN = ethane-1,2-

diamine) complex attached to biotin was isolated and the X-ray crystallographic structure was obtained.[131,132]

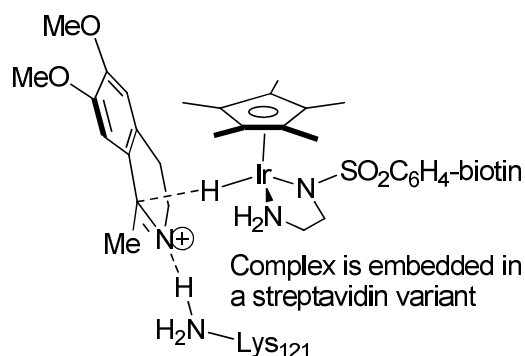


Figure 43

The streptavidin variant is generated as a part of a screen of modifications. In this work, no asymmetric induction was obtained without protein, and the wild-type streptavidin (Sav) gave a reduction product of up to 57% e.e. (*R*). However the S112A mutant of Sav gave an amine in up to 96% e.e. (*R*) and in other cases (e.g. S112K mutant) the enantioselectivity could even be reversed. In addition up to 4000 turnovers of the synthetic enzyme could be achieved.[133-137] Computational and molecular modelling has been applied to this process to aid optimisation.[138]

In parallel work, the synthetic enzyme has been gradually refined through further optimization. In a later paper,[139] human carbonic anhydrase II, was combined with a sulfonamide derived from pyridine/IrCp* to create a catalyst for the ATH of imines. The X-ray structure of a derivative was used to improve the catalytic performance, ultimately achieving 68% e.e. A ribonuclease has also been used as the basis of an artificial amine reductase. In this case the incorporation of a Cp*Ir complex gave an efficient and selective artificial enzyme for imine reduction.[140]

With the most advanced streptavidin variants, the strategy in which a racemic catalyst is converted to a chiral-at-metal complex and then assisted further by residues in the chiral protein, have led to the development of both *R* and *S*- selective synthetic enzymes for imine reduction. Extensive kinetic data has been obtained for these new synthetic enzymes, and computer modelling of the complex structures (which contain four interacting subunits) serves to support and understand the results. An ‘induced lock and key’ where the host protein

structure determines the catalyst structure and the reduction selectivity, is proposed (Figure 44).[141]

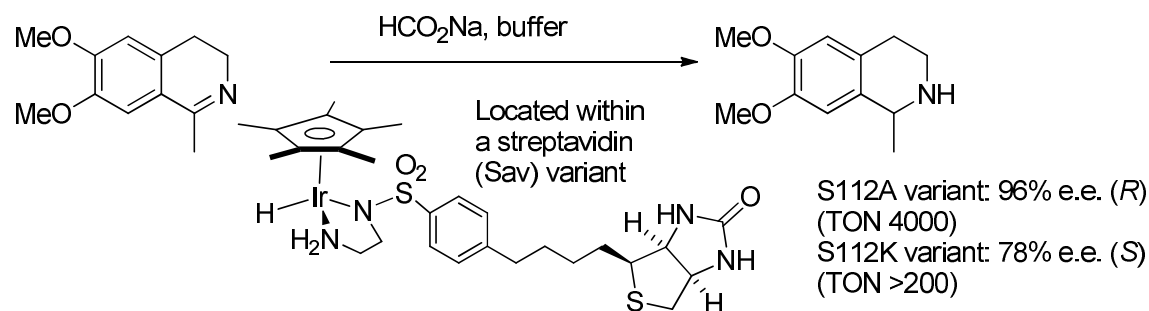


Figure 44

Optimisation of a synthetic enzyme derived from human carbonic anhydrase II has also been achieved in a similar manner, resulting in conversion of a wild type selectivity of 70% e.e. with a TON of 9 to a modified variant with several residue changes which gave a product in 96% e.e. and a TON of 59. Again X-ray crystallographic evidence demonstrated that the piano stool complex was embedded within the protein; which served to influence its configuration and assist in the asymmetric control of hydrogen transfer.[142] An ingenious method for amine deracemisation can be achieved within a cascade of reactions which combines a biocatalyst with the synthetic enzymes created in this work.[143] Related work has been reported on ketones rather than imine, and several informative reviews on Ward *et al.*'s work have been published.[144-148] A related example describing the influence of an external directing group – in this case a homochiral phosphonic acid – on the transfer of hydride from a $\text{Cp}^*/\text{Ir}/\text{TsEN}$ complex to an imine, has been reported. [149] Although hydrogen gas is used as the reducing agent, a similar process of chirality induction takes place at the Ir complex.

2.5 Hydrogen borrowing and organocatalysis.

Although technically a 'hydrogen borrowing' reaction rather than a reduction, a $\text{C}=\text{N}$ reduction is involved at a key stage to good effect in some specific applications where an alcohol is converted to a chiral amine. Cooperative catalysis by iridium complex and a chiral phosphonic acid can lead to asymmetric amines starting from racemic alcohols.[150] Likewise, the use of a chiral phosphonic acid with an Ir/TsDPEN complex gave a very interesting DKR and amination of alcohols in one process; from a mixture of four isomers, one product enantiomer is predominantly formed.[151]

In recent years, several papers have been published on the combination of an organometallic catalyst with a chiral phosphonic acid in order to achieve enantioselective reduction of an imine. This obviates the requirement for a Hantzsch base by replacing it with the combination of an organometallic complex and hydrogen gas. However since these involve the use of hydrogen gas they are technically outside the scope of this review, although a recent overview is highlighted [152] and one example is illustrated (Figure 45).[153]

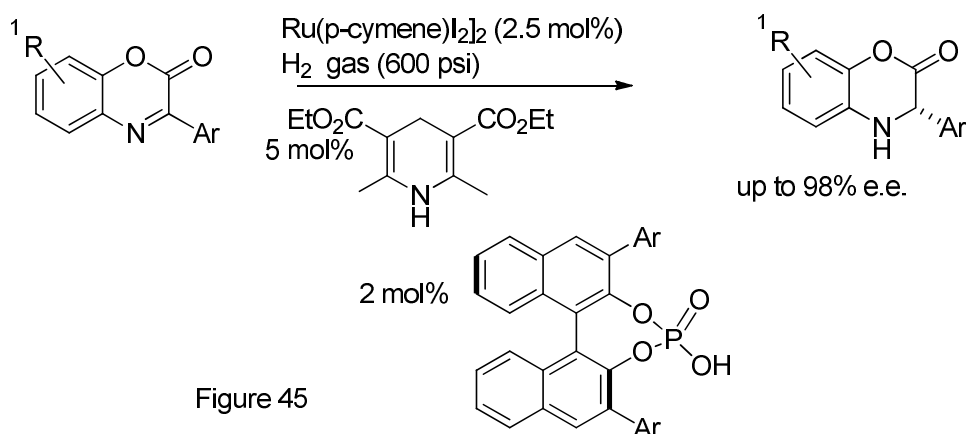


Figure 45

The direct reductive amination of aromatic aldehydes has been achieved with excellent yields using a gold(I) catalyst along with a Hantzsch ester as the hydrogen source under mild reaction conditions.[154] In another example, $B(C_6F_5)_3$ is shown to act as a catalyst for the transfer of hydrogen from a Hantzsch ester to an imine.[155]

3 Meerwein-Ponndorf–Verley (MPV) reductions

The development of asymmetric MPV reactions has been described [156], notably a very selective system based on $Al(III)$ /BINOL complexes has been reported (Figure 46).[157] In this example the ees for all products were determined although only the configuration of the 1-phenylethylamine derivative was established. However the absolute configurations of the other products can be inferred (but are not shown) based on the steric size difference between the substituents flanking the imine in the substrate.

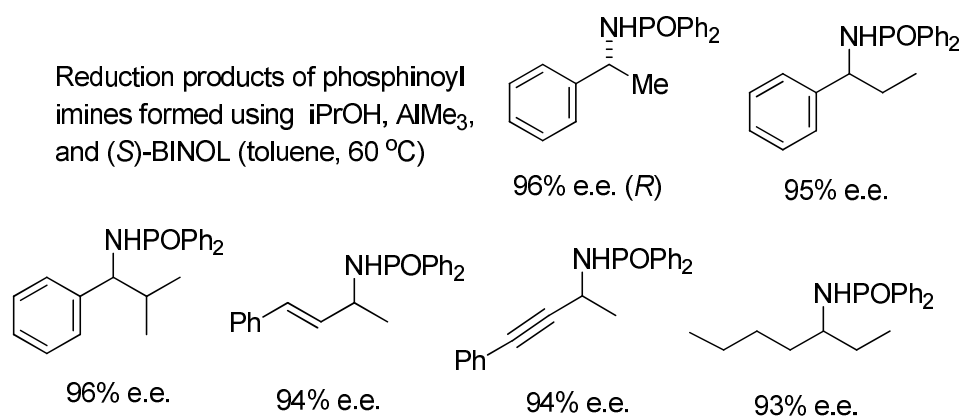


Figure 46

In a recent example, α -silylamines were prepared by MPV-type reduction of α -silylimines. This does produce the amines in up to 99:1 er although it is a stoichiometric rather than catalytic process using a chiral amine as the donor of hydride (Figure 47).[158]

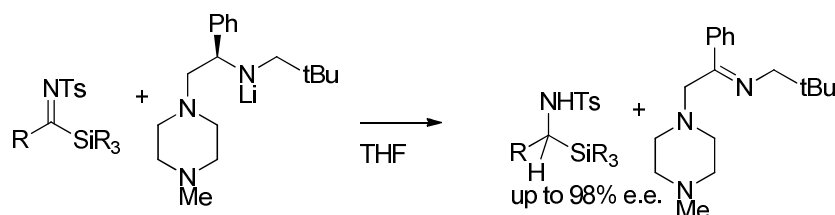


Figure 47

4) Reductive amination reactions.

The Leuckart-Wallach reaction has been reported as being effective for the synthesis of chiral amines, with some very important contributions having been made by Kadyrov and Riermeier, who employed a Ru(II)/BINAP derivative to excellent effect, giving products from acetophenone derivatives in up to 95% e.e. [159]. The simple complex [Cp*Rh(III)Cl₂]₂ can be used to give racemic products.[160] In a recent *related* example, although a hydrogenation rather than a transfer hydrogenation, a BINAP/Pd complex was used to form products of up to 99% e.e. in reductive amination of acetophenones using anilines (Figure 48).[161]

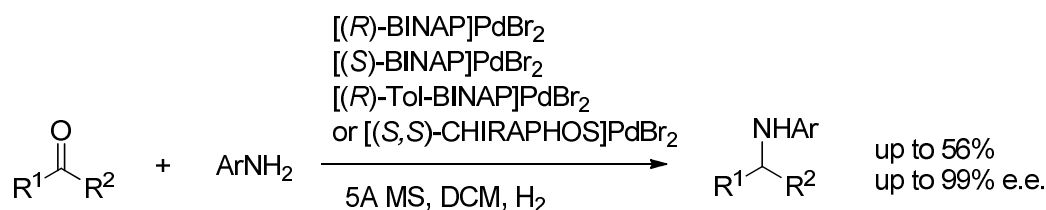
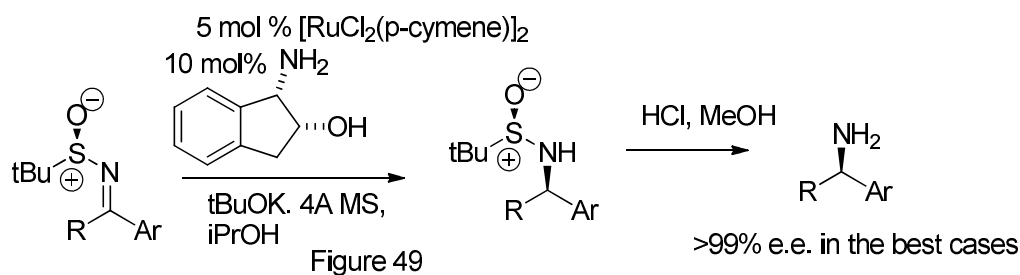


Figure 48

5 Diastereoselective asymmetric reductions

A series of highly selective reactions have been reported by Guijarro *et al.*, where a chiral sulfinyl group directs the ATH of an imine, using either an asymmetric catalyst or a racemic one (Figure 49). Using *cis*-aminoindanol, very selective syntheses of amines are possible,[162-164] and imine formation could be accelerated with microwave irradiation.



However in later work it was found that a non-chiral ligand could also be used – the enantioselectivity being created by the sulfinyl group (Figure 50).[165-167] Microwave radiation can be used to accelerate the reaction.[168]

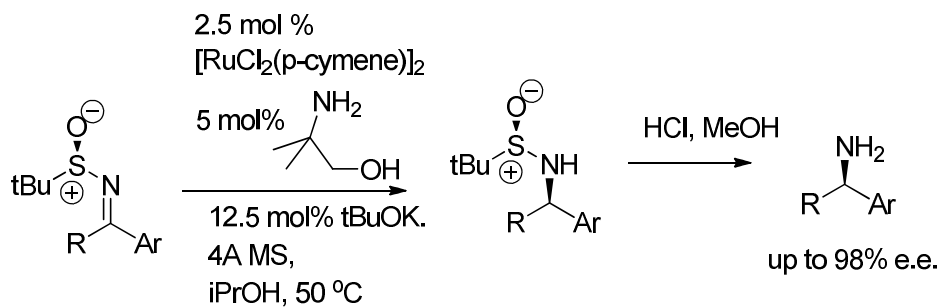


Figure 50

The work has been applied to the synthesis of a series of heterocycles using halide-substituted substrates and then completing the ring synthesis using a base-promoted process, followed by removal of the sulfinyl group. (Figure 51).[169]

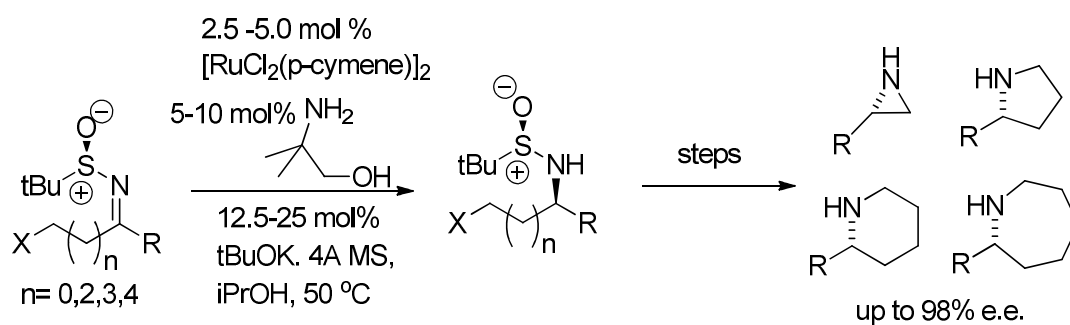


Figure 51

6 Carbene ligand-based catalysts.

A wide range of complexes containing N-heterocyclic carbenes have been used in the TH of imines, and some examples are given in Figure 52, along with an indication of the typical TONs for some of the reductions. In many cases the turnover numbers are impressive.[170-174] The area has been reviewed in some depth.[175-178]

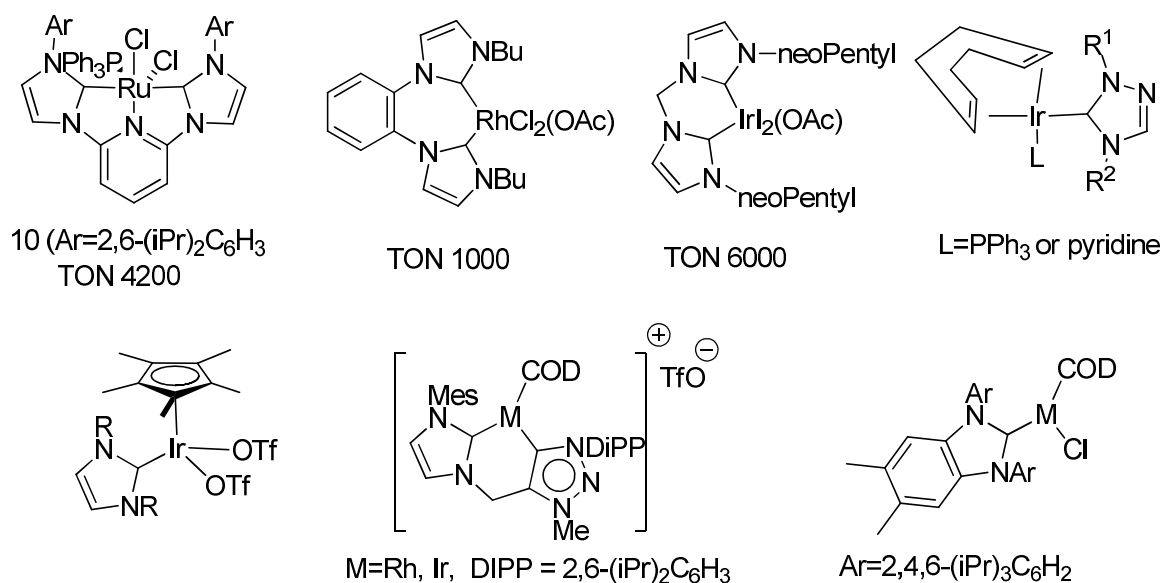


Figure 52: Carbene complexes for the TH of imines.

A carbene derived from triazole was used in IPA with K_2CO_3 as base, for direct reductive amination of aldehydes with primary amines to form secondary amine products.[179] Other recent examples include; i) a base-free catalyzed reduction of a series of $\text{C}=\text{O}$ bonds and of the $\text{C}=\text{N}$ bond of benzylideneaniline (>99% conversion was achieved in 48h, with 0.1 mol% catalyst),[180] ii) heteroditopic dicarbene Rh(I) and Ir (I) complexes containing 1,2,3-triazolylidene–Imidazolylidene ligands, mostly tested on acetophenone but with one imine

example,[181] iii) Ir complexes of N-benzyl substituted N-heterocyclic carbenes where 0.5 mol% catalyst is used with 5% KOH in IPA in reductions to give products in >99% yields[182] and iv) Ir(III) and Ru(II) complexes with 4-acetylbenzyl-N-heterocyclic carbenes which are active at reduction of C=O, C=N and hydrogen borrowing.[183] Half-sandwich Ru(II) picolyl-NHC complexes used to reduce C=O and C=N with just 0.1 mol% catalyst have been reported; the catalyst has a bidentate donor containing an NHC and a pyridine donor and works well in reductions.[184] Similar complexes with hemilabile OMe or pyridine ligands[185] and Ru(II) picolyl-NHC complexes have also been reported.[186]

7 Other non-chiral catalysts.

Several examples of TH of imines have been reported, using a range of complexes, most commonly based on precious metals including Ru, Ir and Rh [187,188] Some reduction aminations of ketones using ammonium formate with some Cp*/Ir complexes have been reported; these are pH dependent with respect to rate.[189] Use has been made of a Ru phenylindenyl chloro di triphenylphosphine complex in catalysis. These have mostly been applied to C=O reduction but examples of imine reduction have also been reported.[190] A novel iminophosphorane-based [P2N2] rhodium complex, representing a very innovative catalyst system, was prepared and used to reduce C=O and C=N bonds.[191]

Some cobalt examples have recently been published; cobalt on a heterogeneous support was used in TH of C=O, C=N and C=C bonds using IPA as the reducing agent.[192] A cobalt catalyst containing a 'PNP' donor structure was used in ATH of a number of imines although the focus was on ketones and aldehydes.[193] Nickel nanoparticles have also been used in imino TH.[194] Studies have been carried out on the activation and deactivation processes of a wide range of Cp*/Rh catalysts which have been developed as valuable supported reagents for C=N reductions in flow systems:[195,196] Efficient and selective TH of pyridines to tetrahydropyridines and piperidines has been achieved using Cp*/Rh diiodide complexes; the method being general and wide in scope.[197] In some cases, an amine/borane complex has been used as the hydrogen source for the reduction.[198] Although there are also examples of where a catalyst is not required.[199]

Imine reductions with Ir catalysts have produced some very important breakthroughs in recent years. Xiao *et al.* reported a new class of cyclometallated Ir-based catalyst e.g. **15**, for imine TH, being active at very low loadings. This has been extensively used in reductive amination

of ketones including carbohydrates FA/TEA.[200] It was found that the control of the pH (best ca. 4.8) is critical for high chemoselectivity and activity, allowing the S/C to be as high as 10,000, and higher than in organic solvents, representing an environmentally friendly catalyst system with broad application (Figure 53).[201] One specific application of the catalyst has been to the transformation of levulinic acid into pyrrolidinones, which was achieved in high efficiency.[202]

The new catalyst **15** and its derivatives is applicable to the synthesis of primary amines by TH of ketones using sodium formate and also FA/TEA in the reductions (Figure 53). FA/TEA improves the results by increasing the acidity relative to ammonium formate alone, which gives products in lower conversions. A large number of examples are given including substituted, aryl and alkyl. Amino acids can be prepared directly from the α -keto acids. Chalcone is reduced to the saturated amine. α -keto ethers work well and this has been used in the synthesis of a antiarrhythmic agent as illustrated in Figure 53.[203] There are few other examples of the synthesis of amino acids through a reductive amination of this type.[204] A phenoxide-chelated Ir complex – **16** in Figure 54 has also been prepared and demonstrated to be capable of C=N bond reduction by both hydrogenation and transfer hydrogenation via reductive amination.[205]

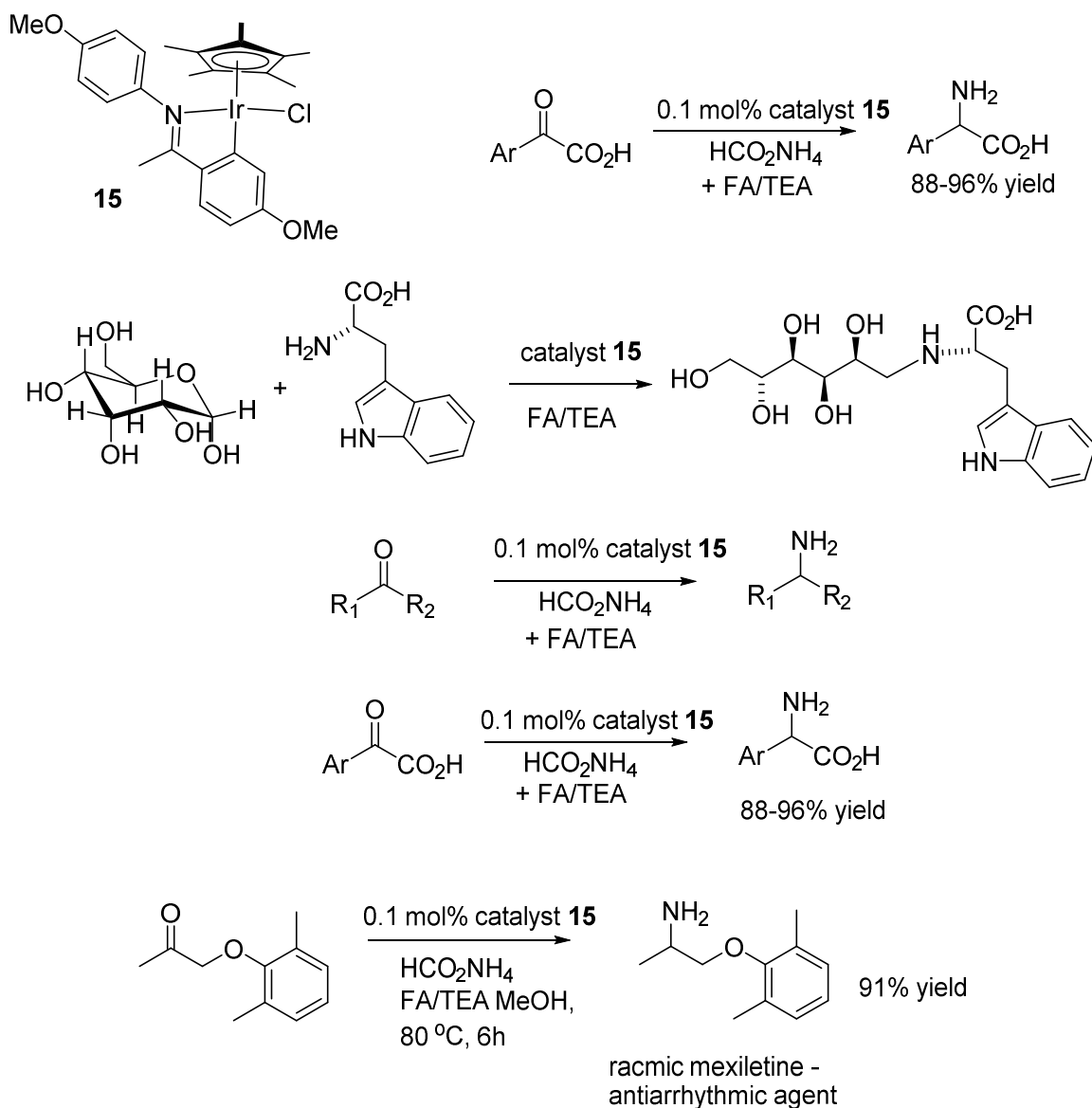


Figure 53

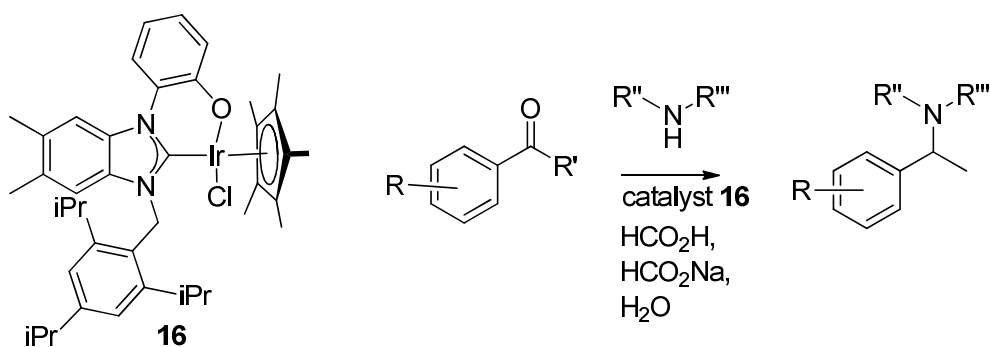


Figure 54

The iridicyclic catalysts also catalyse the TH of N-heterocycles (including quinolines, isoquinolines, indoles and pyridinium salts) in water under mild conditions – a solution of

formic acid and sodium formate is employed in the reaction. TONs of up to 7500 and catalyst loadings as low as 0.01 mol% were used.[206]

Another potentially very important development in TH reactions is reduction of NAD⁺ to NADH by half sandwich complexes of precious metals, which has been shown to also take place within living cells [207-211]. It has been demonstrated that the activity of Ru/TsEN complexes against human ovarian cancer cells is increased by as much as 50x when non-toxic doses of formate are added.[211]

8 Conclusion

In conclusion, a very wide range of new chemistry has been developed for the transfer hydrogenation of C=N bonds. Several new classes of catalyst have been reported, including several asymmetric catalysts, and applications to a large number of target molecules, notably including pharmaceutical intermediates, have been reported. This area looks set for significant continued growth in future years.

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